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# The R. E. DYER LECTURE

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# *Genetic Control of Metabolism*

By

George W. Beadle, Ph. D.

Kerckhoff Laboratories of Biology
California Institute of Technology

Presented June 21, 1951

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*The first*

# R. E. DYER LECTURE

*Awarded to*

George W. Beadle, Ph. D.

JUNE 21, 1951

This award, honoring Dr. Rolla E. Dyer on the occasion of his retirement from the Public Health Service, was established in 1950 by his friends and colleagues in medical science. It is administered by the National Institutes of Health, Public Health Service, Federal Security Agency.

# *Opening remarks at the first R. E. Dyer lecture by Dr. W. H. Sebrell, Jr., Director, National Institutes of Health, of the Public Health Service*

It is a great privilege to serve as your chairman on the occasion of the first R. E. Dyer lecture.

The lectureship committee has asked me to express its sincere appreciation to Admiral Swanson for his kindness in making the auditorium of the National Naval Medical Center available to us. Immediately after the selection of the first Dyer lecturer was announced, it was obvious to the committee that a larger auditorium than is available at the National Institutes of Health would be required for the occasion.

The inclination is strong for me to speak at length about the man in whose honor this lecture has been established and with whom it has been my good fortune to be associated for many years. However, I note that Dr. Dyer is in the audience, and in deference to him, I will content myself simply by asking him to rise.

Since this is the first of the Dyer lectures, it seems appropriate to give for the record a brief description of their origin. When it was learned that Dr. Dyer, Director of the National Institutes of Health, was to retire, a group of his friends and colleagues decided that a lectureship fund would be a fitting tribute to his many years of noteworthy service to medical science. Under the leadership of Gen. James Stevens Simmons and Dr. Lowell T. Coggeshall, the lecture-

ship was established to recognize research achievement in the medical and biological sciences.

Selection of tonight's lecturer was made from a large panel of names nominated by a committee of scientists, in keeping with the criteria set forth by those who established the lectureship. The committee has consulted many individuals in the medical and biological sciences and related disciplines, among others the presidents of the several professional societies in which Dr. Dyer has been most actively interested throughout his career.

General Simmons, who will present the speaker to you, needs little introduction to an audience such as this. He is well known for his endeavors in public health and preventive medicine, tropical medicine, and experimental bacteriology. In his present position as dean of the Harvard University School of Public Health, he occupies in scholarly yet very human fashion an important place in the scientific community.

From 1940 to 1946, as Chief of the Division of Preventive Medicine, Office of the Surgeon General of the Army, he worked diligently to improve the health of our Armed Forces. For his efforts here and elsewhere he has been commended by many medical, military, and civic organizations. A long-time friend and colleague of Dr. Dyer and a new friend of the first recipient of the Dyer lectureship award, he is well fitted for the pleasant task of introducing the speaker of the evening.

# *Introduction of Dr. Beadle by James Stevens Simmons, M. D., Brig. General USA (Ret.), Dean of the Harvard School of Public Health*

It is a pleasure to present the first recipient of the R. E. Dyer lectureship—Dr. George Wells Beadle. Dr. Beadle is a distinguished geneticist and chairman of the Biology Division of the California Institute of Technology. He is widely recognized for his many contributions in the field of biochemical genetics, particularly for his demonstration of the relationship of genes to specific chemical reactions.

Dr. Beadle will discuss with us tonight the current status of his interesting investigations of the biochemical activity of chromosomes.

Dr. Beadle received his bachelor of science and master of science degrees from the University of Nebraska, his doctor of philosophy degree from Cornell, and his doctor of science degree from Yale. He is a former National Research Council fellow at the California Institute of Technology, and served with distinction as guest investigator at the Institut de Biologie in Paris. Dr. Beadle has been a member of the faculties at Cornell, Illinois, Harvard, Stanford, and the California Institute of Technology. Since 1946 he has been professor of biology and chairman of that Biology Division at the latter institution. In addition to his basic research in genetics and biology, Dr. Beadle is well known to many of you as the coauthor, with Alfred H. Sturtevant of the text, *An Introduction to Genetics.*

Our speaker received the Lasker award in 1950 "for his outstanding and fundamental contributions to the understanding of genetic control of metabolic processes." For several years Dr. Beadle and his associates have been investigating the basic chemical mechanisms of heredity variation. Turning away from the classical approaches to genetics, this group has concerned itself with the effects of changes produced experimentally in genes upon specific metabolic activities in the cell. Working with a common mold (Neurospora), they have demonstrated that particular genes control various individual biochemical reactions of the cell, and that consequently the loss of a particular gene results in transmission to subsequent generations of a characteristic disturbance of metabolic activity. The potentialities of this work are exciting. Fulfillment of the implications of these pioneer studies may lead to a better understanding of human constitution as related to the vital problems of host resistance and susceptibility in both metabolic and infectious disease.

Dr. Beadle is also recognized among his fellow scientists for his scholarly reviews in the field of genetics. Many of his scientific papers have appeared in leading professional journals and in the *Annual Review of Biochemistry.*

He believes that biochemists have begun to think in terms of genes because it has been demonstrated to them that the chemical reactions which make up living systems are under the fairly immediate supervision of these units of inheritance, and also because genetics provides a powerful tool with which much can be learned about metabolic systems.

In recognition of his outstanding contributions, Dr. Beadle was elected president of the Genetics Society of America in 1946, and the following year he was made president of the Western Society of Naturalists. He has also served as a consultant to a number of Government agencies, including the Atomic Energy Commission, Office of Scientific Research and Development, The United States Army, the United States Navy, and the Office of Production Research and Development.

Dr. Beadle's principal fields of interest are the cytology of maize; genetics of maize; physiological genetics of Drosophila; and chemical genetics of Neurospora.

He is a member of the National Academy of Sciences, the American Philosophical Society, and many other learned societies and associations.

I feel sure that the selection of Dr. Beadle as the first recipient of the R. E. Dyer lectureship is highly appropriate, and that the subject which Dr. Beadle will discuss tonight is in keeping with the broad vision of my distinguished friend, Rolla Dyer, for whom this lectureship is named.



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# Genetic Control of Metabolism

G. W. Beadle, Ph. D.

*Kerckhoff Laboratories of Biology, California Institute of Technology*

Charles Darwin's conception of the origin of species and their gradual further selection and inheritance represents one of the two great revolutionary advances in biological thinking that have taken place within the past hundred years. The other equally important related development was the discovery of particulate inheritance by Gregor Mendel. Together Darwinism and Mendelism have changed our ways of thinking about living systems. Indeed, they have changed our very ways of life for they have become indispensable parts of the basic knowledge so important in both our material and intellectual progress.

The revolutionary unification of the biological sciences initiated by Darwin and Mendel is still actively under way. Discoveries are reported almost daily that help us to see more clearly how living systems function, reproduce, and evolve. Especially through work on the simplest of known living systems, the viruses, we are beginning to see more clearly what are the irreducible properties of the living state and how, in principle, systems with these properties might have originated from nonliving precursors and given rise to the great variety of complex organisms that inhabit the earth today.

*Genes as units of inheritance and of function.*—The mechanism by which genes, the units of inheritance of Mendel, are transmitted from generation to generation in man is well illustrated by the disease hemophilia. This trait,

which occurs in about 1 male in 50,000 in our species, was not described in any detail in medical literature until shortly after 1800. Its inheritance was not understood until after Morgan's 1910 discovery of sex-linkage in the fruitfly. It then became obvious that hemophilia in man follows the same pattern of inheritance. It results from a defect in a gene carried in the X chromosome. The mutant form of this gene is recessive to its normal counterpart. This means that a woman may carry the gene defect in one of her two X chromosomes and transmit it even though she herself shows no sign of the defect. Half her sons receive from her an X chromosome with a defective gene and from their father a Y chromosome that carries no normal form of the hemophilia gene; they are bleeders.

Through the work of Lawrence and Craddock we fortunately know something about the chemical basis of hemophilia. There is in blood of normal individuals a serum protein of the gamma globulin fraction that somehow plays a role in the clotting mechanism. In hemophiliacs this specific protein appears to be either absent or greatly reduced in its blood-clotting activity. Evidently the normal form of the hemophilia gene is essential for the presence or at least the activity of the specific gamma globulin concerned in blood clotting.

Another case in which there appears to be a close relation between a gene and a specific protein concerns the inherited human blood disease sickle cell anemia. This has been studied genetically by Prof. James Neel at the University of Michigan and chemically by Prof. Linus Pauling and collaborators at the California Institute of Technology. It is found that when a defective form of a particular gene—carried in a non-sex-determining chromosome in this instance—replaces its normal counterpart, there is a change in the electrophoretic mobility of the hemoglobin of the blood cells. Since there are two representatives of each non-sex-linked gene present in each cell of an individual, there are two types of individuals with the defective gene concerned with blood-cell sickling: those with one defective and one normal form of this gene in each cell and those

with two defective genes per cell. The first type possesses red cells that show characteristic distortion known as sickling only at abnormally low oxygen tensions. They are said to possess the sickle-cell trait and they show only relatively mild symptoms. The second type, in which defective genes are simultaneously inherited from both parents, shows severe sickle-cell anemia in which sickling and destruction of red cells occur at physiological oxygen tensions. The result of this severe form of the disease is usually death before maturity.

Physical chemical studies of the hemoglobin of the three groups—normal persons, those with sickle-cell trait and those with sickle-cell anemia—show that in the first class all hemoglobin molecules are normal, in the second approximately half are normal and half differ from normal in mobility, while in the last group all hemoglobin molecules show altered electrophoretic migration. Aside from the charge difference in the two types of hemoglobin molecules they appear to be very similar. The heme portions of the hemoglobins are not detectably different chemically. There is no clearly detectable difference in amino acid composition of the globins.

It appears that the normal form gene concerned with the sickle cell character is essential for the formation of normal hemoglobin molecules, while its mutant form conditions the presence of modified molecules. When both forms are simultaneously present in a single cell, both kinds of molecules are produced. A reasonable interpretation of these relations is that there is an intimate relation between the gene and the specific property of the hemoglobin molecules having to do with the effective charge carried by them.

There are other inherited diseases in man that suggest a close relation between genes and protein specificities. In alcaptonuria, for example, in which 2,5-dihydroxy-phenylacetic acid (alcapton) is not metabolized, but instead is excreted in the urine, there is evidence that, in the absence of the normal form of a specific gene, the enzyme that normally catalyzes the cleavage of the ring of alcapton is absent or inactive and that as a consequence alcapton

accumulates. Hereditary idiocy, associated with inability to oxidize phenylpyruvic acid to its para-hydroxy analog, is a disease metabolically closely related to alcaptonuria. As a result of this genetic block in metabolism, phenylpyruvic acid is excreted in the urine. Although in this case there is no direct knowledge that the interrupted reaction is normally enzymatically catalyzed, it seems likely that the same type of gene enzyme relation holds here as in alcaptonuria.

Galactosemica is an hereditary inability to utilize the specific sugar galactose. If glucose is substituted for galactose in the diet of affected babies, recovery is dramatic. Otherwise death may ensue.

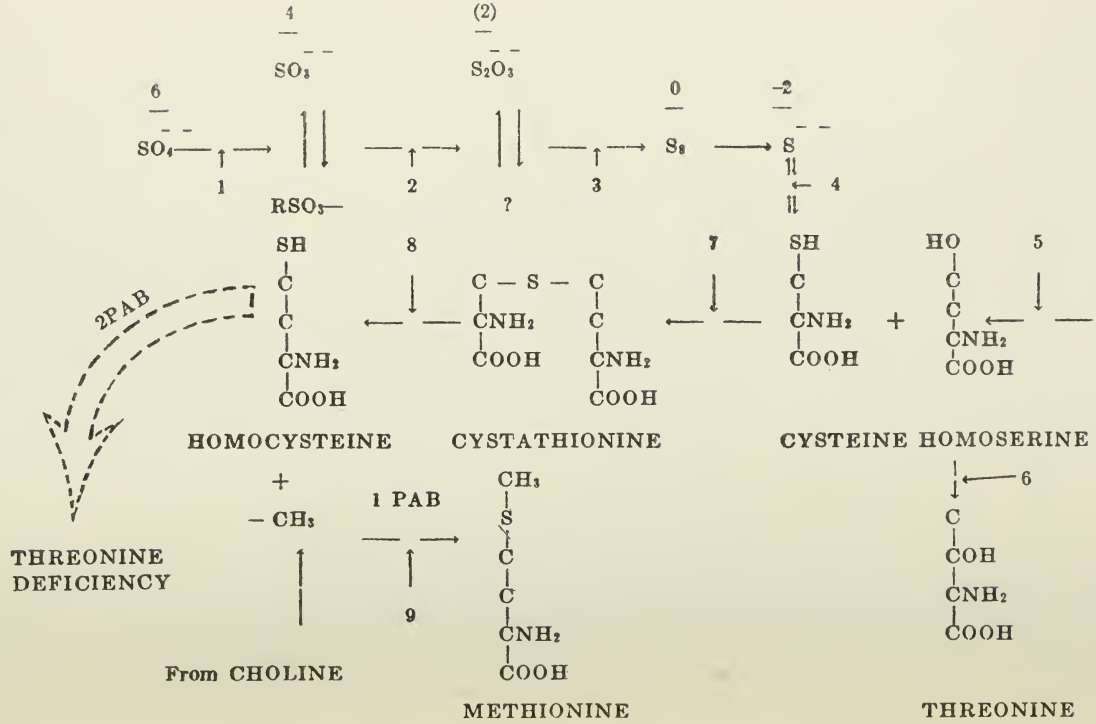
Because the expression of the disease is strongly subject to both genetic and environmental modifying factors and because it often develops in middle or late life, the inheritance of diabetes mellitus is not clear. It is probable, nevertheless, that the continued production of the normal amount of insulin is immediately dependent on the normal form of a specific gene.

Other gene-controlled steps in metabolism in man are known. In other organisms more favorable for genetic and biochemical study many examples similar in principle could be cited. In the bread mold *Neurospora crassa* many hundreds of specific metabolic defects have been produced through gene mutation. The work on these has been reviewed several times, so there would be little point in recounting it in detail here. It suffices to say that the genetic and biochemical behavior of most of the mutant types in which biosynthetic processes are interrupted is consistent with the hypothesis that enzymes, the specificities of which are gene-directed, serve as intermediaries between the genes and specific chemical reactions.

Many of the principles involved in the Neurospora work are illustrated by a group of mutant types in which reactions concerned with sulfur metabolism are interrupted. Studies of these strains by Prof. Norman H. Horowitz, Dr. H. J. Teas, Dr. Marguerite Fling, Dr. B. O. Phinney, Miss Helen

Buss and others has led to the scheme of sulfur metabolism illustrated in figure 1. The first isolation of cystathionine from a biological source was made from a mutant strain of Neurospora in which gene 8 was carried in mutant form. Similarly, if gene 7 is mutated, the formation of cystathionine is blocked and homoserine is accumulated.

Prof. Sterling Emerson has studied a mutant strain of Neurospora that under certain conditions of culture grows with a sulfonamide supplement but not without. Furthermore, under specific circumstances this strain can be inhibited in growth by the addition to the medium of *p*-aminobenzoic acid (PAB). This paradoxical situation in which the normal roles of a vitamin and a growth inhibitor seem to be reversed is explained by Emerson on the assumption that in the mutant strain a PAB-containing enzyme catalyzes a reaction that does not occur normally and in which homocysteine is used in some manner to bring about a threonine deficiency. The amount of PAB required to catalyze this deleterious reaction is more than that necessary to catalyze a reaction in the methylation of homocysteine to give the essential amino acid methionine—two units as compared with one in the scheme shown in figure 1. The normal wild-type strain is assumed to make at least three units of PAB but does not use any to promote the unfavorable reaction. The mutant strain, on the other hand, uses one unit for the favorable reaction and two units for the reaction leading to a threonine deficiency. If in the mutant strain PAB synthesis is genetically blocked by introducing a second mutant gene through genetic recombination and only one unit of PAB is supplied in the culture medium, growth occurs without the addition of a sulfonamide. There is evidence that the sulfonamide-requiring mutant does not make more PAB than normal but has become sensitive to this vitamin through a mechanism by which it uses the normal excess of PAB to promote the harmful reaction. This reaction can be blocked by the addition of a limited amount of a sulfonamide because presumably a lesser amount of this drug is needed to competitively inhibit the deleterious reaction than is needed to interfere with the beneficial methylation reaction. A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second method of bringing about growth of the sulfonamide-requiring mutant without using a sulfonamide involves making up the threonine deficiency through a supplement of this amino acid in the medium.

I have described Emerson's studies on the sulfonamide-requiring mutant in some detail because they throw much light on the intimate biochemical action of the sulfonamides. So far as I am aware more is known about the mechanism of action of the sulfonamides than about any other class of drugs. It is of considerable interest that studies on the biochemical genetics of the bread mold have not only added to this knowledge but have convincingly and spectacularly confirmed the hypothesis that the sulfonamides act through inhibition of an essential enzyme action by competition with the vitamin para-aminobenzoic acid.

*The genes of Bacteria.*—Following the production and study of a large number of so-called biochemical mutants in Neurospora in which specific biosynthetic reactions are blocked, similar mutants were produced and studied in essentially the same way in bacteria. In *Escherichia coli,* for example, Prof. E. L. Tatum, Prof. Joshua Lederberg, Dr. B. D. Davis and others have produced a series of mutant types that parallel in remarkable detail the biochemical characteristics of the Neurospora mutants. This parallelism in itself strongly suggests that bacteria possess the same mutational and functional units, i. e., genes, as does Neurospora. This supposition was proved to be correct in a very convincing way by Professor Lederberg and Professor Tatum in their studies of recombination in bacteria. These studies combined with the recent advances in bacterial cytology which show that many bacteria possess chromosome-like sub-units that are distributed to daughter cells by a mitosis-like mechanism should convince the most skeptical critic of the existence in bacteria of gene-like units of inheritance, function, and mutation that in all essential respects are like the genes of higher organisms.

It has become increasingly clear in recent years that the protoplasms of diverse organisms are remarkably similar in many respects. Their proteins are constructed of the same amino acids. They utilize many of the same vitamins in essentially the same way. The same purines and pyrimidines make up their nucleic acids. Several of the vitamins now known to be essential to the functioning of higher plants and animals were discovered as growth factors for microorganisms. In this connection it is of considerable interest that Dr. B. D. Davis of the United States Public Health Service has recently discovered a new bacterial vitamin *p*-hydroxybenzoic acid, by determining that it was a highly active growth factor for a mutant strain of *Escherichia coli* that had lost the ability to grow on the unsupplemented basal medium regularly used for this organism.

In higher plants and animals it has so far not been possible to direct the mutation process in any precise way. In bacteria, however, there is reason to believe that this may be possible in at least certain instances. I refer to the work on the transforming principles of pneumococci as studied by Dr. O. T. Avery of the Rockefeller Institute for Medical Research, his associates and his successors in this field of investigation. Here, as is well known, there appear to be type-specific nucleic acids that can be transferred from a strain possessing them to one in which there is a specific deficiency. The transformed strain then continues to elaborate nucleic acid of the same specificity as that used to direct the transformation. In this way it is possible to transform in a controlled way one serological type of pneumococcus into another. It seems possible that the transformation involved the actual replacement from the outside of a missing nucleic acid component of a specific gene. The developments now taking place in this field of biology are with little doubt of tremendous importance to both theoretical and applied biological fields.

*Gene nature and gene action.*—Genes appear to be largely, if not entirely, made up of nucleoproteins. One of their basic properties is the ability systematically to direct the synthesis of replicas of themselves from a heterogeneous

array of simpler substances. In addition to accomplishing this notable feat—an ability possessed only by living systems—it is believed by a number of biologists that genes function in a primary way in directing the specificities of nongenic proteins and possibly of other large molecules with high degrees of biological specificity. It has often been suggested that the mechanism by which genes reproduce may be essentially the same as that by which they direct the specificities of nongenic substances. Unfortunately we do not understand either of these processes. It has been pointed out by Prof. Sewell Wright and others that the difficulties are many in imaging that genes duplicate themselves and direct the synthesis of nongenic specific proteins in a step-by-step process during which specificities gradually increase. It seems much more likely that genes both multiply and direct the formation of their primary nongenic products by a model-copy mechanism of some kind.

In thinking about the manner in which genes produce their effects it is often assumed that a given gene is involved in a primary way with but a single enzyme—a concept that in recent years has come to be known as the one gene-one enzyme hypothesis—or, to make it more general, the one gene-one primary function hypothesis. This hypothesis has recently been examined critically by Prof. N. H. Horowitz and Dr. Urs Leupold, using so-called temperature mutants of *Neurospora crassa* and *Escherichia coli*, that is, mutant types that grow over one part of the normal temperature range of the organism without a growth-factor supplement but fail to grow on unsupplemented medium over another part of the temperature range. By recovering such mutant strains at the temperature at which they grow without supplements and testing them for reparability at the temperature at which growth fails on an unsupplemented medium, it is possible to classify a presumed random sample of genes for reparability or irreparability of their functions. It was found that less than half the gene functions so sampled in Neurospora and less than one-fourth in *E. coli* were irreparable. This means that the proportion of genes in which mutations can impair more than a single function is low. In other words the high proportion of

mutant genes found in which only a single function has been abolished cannot be due to the simple selective elimination of mutant genes with two or more impaired functions.

A highly significant suggestion made by Horowitz and Leupold is that the synthesis of a protein molecule must, in general, be brought about by an enzyme working directly on amino acids or relatively simple derivatives of them. If proteins were synthesized by an alternative stepwise process through peptides of larger and larger size, it seems almost certain that mutational losses of gene function would more frequently be irreparable than the data indicate them to be. This argument parallels closely that of Sewell Wright referred to above, to the effect that if genes directed the successive aggregations of compounds of increasing size in such a way that specificity increased with each step, mutation in one gene would be expected to cause mutation in other genes in which the specific building blocks produced by the first gene were component parts. In general, of course, this is not the case.

*Genes of viruses.*—If Rickettsias and viruses have had their evolutionary origins through gradual loss of function and simplification of structure, as Dr. F. M. Burnet and others have postulated, we should expect them to be made up of gene-like subunits. For if our hypothesis is correct that genes represent the essential pattern molecules of living systems possessing the properties of self-duplication and mutation, it should be possible for a parasite to become as simple as a single gene and still continue its existence.

The Rickettsias have not been studied genetically in the detail in which bacteria and higher forms have. But the bacterial viruses that multiply in *Escherichia coli* have been. Prof. Max Delbrück, Prof. S. E. Luria, Dr. A. D. Hershey and others have found that these viruses are capable of mutating with respect to host range, rate of lysis and other properties. They have shown further that if a single bacterial cell is simultaneously infected with two different mutant particles of an originally single virus strain, there

often appear after lysis of the bacterial cell not only offspring like the parent viruses with which the cell was infected, but also two new types of virus, one like the normal nonmutant strain, and one possessing within each virus particle the two mutant characters. In principle such recombination of properties is exactly like the recombination of genes known in higher forms. Through recombination studies it can be shown that there may be as many as a dozen such genelike units per virus particle.

It is now clear, therefore, that insofar as they contain genelike subunits bacterial viruses are very much like bacteria or bread mold or men. They are stripped of a great deal of structure and functional complexities of higher forms but they still possess the two essential attributes that one may say define the living state, that is, the ability to reproduce when placed in an appropriate environment and the ability to mutate. The one property enables them to perpetuate their kind, the other permits their survival in evolutionary competition with the hosts in which they grow.

Whether other viruses possess genelike subunits and whether they are viruses that have become reduced to a simpler state, genetically speaking, than the bacterial viruses is not known. But it is known that many of them are mutable. It seems most probable that the phenomena of recombination and of mutation in disease-producing viruses must be of significance in determining their success relative to that of their hosts. One is strongly tempted to suggest that the world's great epidemics involving man and other organisms may have resulted from mutational or recombination changes in the pathogens that caused them.

Conclusion.—I should like to conclude by emphasizing that the gene theory has become one of the great unifying principles of modern biology. Far from being merely pawns with which the geneticist plays games to amuse himself, genes are the units that were aggregated, mutated, and recombined to give rise to the countless forms of subcellular, unicellular, and multicellular forms of life that exist now or

have existed in the last 2 billion years. They are the sets of pattern molecules or templates with which each of us started development as a fertilized egg and they represent the essential self-duplicating units that we pass on to our children through the nuclei of our eggs and sperm.

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FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE PUBLICATION NO. 142
NATIONAL INSTITUTES OF HEALTH

UNITED STATES GOVERNMENT PRINTING OFFICE, WASHINGTON : 1952

For sale by the Superintendent of Documents, U. S. Government Printing Office
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